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**Toni Choueiri, MD**  
 Dana-Farber Cancer Institute  
 Boston, MA



**David Braun MD, PhD**  
 Dana-Farber Cancer Institute  
 Boston, MA



**Moshe Ornstein, MD, MA**  
 Cleveland Clinic Taussig  
 Cancer Center  
 Cleveland, OH



**Tian Zhang MD, MHS**  
 UT Southwestern Medical Center  
 Dallas, TX



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# The Shifting Treatment Paradigm for Advanced Renal Cell Carcinoma

**D**ifferent oncology clinicians may diverge in their treatment approaches to advanced renal cell carcinoma (RCC) due to multiple options being considered standard-of-care therapies. Combination therapies have made great strides against the former standard of care, sunitinib (Sutent), and although investigators have not landed on a cure, many therapies are extending survival and sometimes improving patient quality of life as well.

At an *Around the Practice* presentation hosted by CancerNetwork®, a panel of experts who were moderated by **Toni Choueiri, MD**, director of the Lank Center for Genitourinary Oncology, director of the Kidney Cancer Center at Dana-Farber Cancer Institute, and the Jerome and Nancy Kohlberg Chair and Professor of Medicine at Harvard Medical School in Boston, Massachusetts, discussed these topics by reviewing available data from recent conferences as well as current challenges in the treatment of 2 patients with metastatic renal cell cancer.

## Frontline Options in RCC

Choueiri started the discussion reviewing recent clinical trials to change the treatment landscape in advanced RCC.

**Tian Zhang MD, MHS**, associate professor

in the Department of Internal Medicine at UT Southwestern Medical Center in Dallas, Texas, discussed the phase 3 CheckMate 9ER trial (NCT03141177), which examined the combination of nivolumab (Opdivo) plus cabozantinib (Cabometyx) vs standard of care sunitinib (Sutent), whose results were published in the *New England Journal of Medicine* in early 2021.<sup>1</sup> The primary end point of progression-free survival (PFS) in the intention-to-treat population showed a median of 16.6 months for patients receiving nivolumab plus cabozantinib compared with 8.3 months for the sunitinib arm, for a 49% reduction in the risk of disease progression or death (HR, 0.51; 95% CI, 0.41-0.64;  $P < .001$ ). For the secondary end point of overall survival (OS), the rate at 12 months in the nivolumab plus cabozantinib arm was 85.7% vs 75.6% for the sunitinib cohort (HR, 0.60; 95% CI, 0.40-0.89;  $P = .001$ ). The objective response rates (ORRs) were 55.7% and 27.1%, respectively ( $P < .001$ ).

Zhang also highlighted a trial update that was presented at the 2021 American Society of Clinical Oncology Annual Meeting (ASCO 2021), which looked at the International Metastatic RCC Database Consortium (IMDC) subgroups for risk status and found that all patient groups benefited from nivolumab plus

cabozantinib over sunitinib, regardless of statuses in intermediate- or poor-risk disease groups. She said most subgroups saw a doubling of PFS along with OS improvements.<sup>2</sup>

Moshe Ornstein, MD, MA, looked at data from the CheckMate 214 trial (NCT02231749) of nivolumab plus ipilimumab (Yervoy) or sunitinib in patients with treatment-naïve RCC, particularly the 42-month follow-up that was presented at ASCO 2021.<sup>3</sup>

“CheckMate 214 really revolutionized the field of kidney cancer treatment in the first-line setting,” he said. “It was the first and only immune-oncology (IO)-based combination to be approved in this setting. The other combinations discussed in this presentation are IO/TKIs (immune-oncology/tyrosine kinase inhibitors),” he said. Published trial data from 2018 showed that at the 25.2-month median follow-up for intermediate- and poor-risk patients, the 18-month OS rate was 75% for the combination vs only 60% for sunitinib (HR, 0.63; 99.8% CI, 0.44-0.89;  $P < .001$ ).<sup>4</sup> The median OS was not reached with the combination and was 26.0 months with sunitinib. The ORRs were 42% vs 27%, and median PFS was 11.6 months vs 8.4 months, respectively (HR, 0.82; 99.1% CI, 0.63-1.05;  $P = .03$ ).

“What is great about this combination and what really led to the approval in intermediate- and poor-risk [disease] is that these results seem to stand up over the test of time, both at the 25-month follow-up, which was the initial presentation, [and] the 42-month follow-up,” Ornstein said. “Approximately 30% of patients are still progression free at around 5 years. This is the only IO combination that is a standard of care in the frontline setting for treatment-naïve patients.”

Choueiri then asked David Braun MD, PhD, physician at Dana-Farber Cancer Institute and instructor in medicine at Harvard Medical School, to share an overview of the phase 3 KEYNOTE-426

trial (NCT02853331), which tested pembrolizumab (Keytruda) plus axitinib (Inlyta) vs sunitinib in the frontline setting for advanced RCC.<sup>5</sup> This landmark study led the pack in combining IO plus tyrosine kinase inhibitor (TKI) therapy for RCC, with an anti-PD-1 antibody plus a specific VEGFR TKI. Initial findings, published in 2019, demonstrated superiority across the board, with an OS rate at 12 months of 89.9% for the combination group compared with 78.3% for the sunitinib group, for a total reduction in the risk of death of 47% (HR, 0.53; 95% CI, 0.38-0.74;  $P < .001$ ). Corresponding median PFS was 15.1 months and 11.1 months, respectively (HR, 0.69; 95% CI, 0.57-0.84;  $P < .001$ ). An interim analysis published in 2020 showed that the combination continued to have superior outcomes over sunitinib, supporting first-line treatment as standard of care.<sup>6</sup>

Though Braun said it has a durable response, “the benefits have gotten a little bit smaller over time,” as the hazard ratio for OS was 0.73 at a median follow-up of 30.6 months, for a total risk reduction now of just 27%. At ASCO 2021, the 42-month follow-up data revealed no big changes and that OS results were within the range of benefit.<sup>7</sup>

“The question in my mind is [whether these results are] a bit of a canary in a coal mine for IO plus TKI in terms of whether there’s that same durability that we see with the ipilimumab-based combination,” Braun said. However, he noted that it is an attractive first-line option for many with advanced clear cell kidney cancers.

Choueiri then discussed the phase 3 CLEAR trial (NCT02811861) that included 3 treatment arms: lenvatinib (Lenvima) plus pembrolizumab, lenvatinib plus everolimus (Afinitor), or sunitinib as the control arm.<sup>8</sup> “This is the new kid on the block,” he said. The study showed the longest median PFS was with lenvatinib and pembrolizumab at 23.9 months vs 9.2 months with sunitinib (HR, 0.39; 95% CI, 0.32-0.49;  $P < .001$ ); for lenvatinib and everolimus,

the median PFS was 14.7 months (HR, 0.65; 95% CI, 0.53-0.80;  $P < .001$ ). Median OS was significantly improved with lenvatinib plus pembrolizumab (HR, 0.66; 95% CI, 0.49-0.88;  $P = .005$ ), but lenvatinib plus everolimus failed to result in the same benefit over sunitinib (HR, 1.15; 95% CI, 0.88-1.50;  $P = .3$ ). As a result, the lenvatinib/pembrolizumab combination was approved in August 2021 as frontline systemic therapy for patients with RCC.<sup>9</sup>

### Case of Frontline RCC

Choueiri brought the conversation to its practical application with a patient case.

#### CASE 1

- A 65-year-old man presented with a 3-month history of fatigue, lower back pain, and unintentional weight loss.
- Medical history: significant for hypertension that is well controlled with medication
- CT of the chest/abdomen/pelvis: left-sided 6.5-cm renal mass; para-aortic lymph node involvement; and liver metastases
- The patient underwent radical left nephrectomy and was found to have Fuhrman grade 4 clear cell carcinoma without sarcomatoid features.
- Karnofsky performance score (KPS): 75%
- IMDC risk score: poor

In response to an audience poll on frontline treatment options, 46% of participants would treat this patient with ipilimumab/nivolumab.

Zhang said they are all good treatments, but when she treats disease in the first line, she chooses IO-based treatments for IMDC intermediate- and poor-risk

disease. Zhang also considers tumor burden and how quickly she needs to achieve disease control. If that is the deal breaker, she will select a VEGF/TKI combination for potentially better disease control instead of ipilimumab/nivolumab. Given the location of the patient's masses and since the patient is not seemingly symptomatic, she would also prioritize ipilimumab/nivolumab.

Ornstein said he would also prefer an IO-based combination. However, he noted that the patient seems to be symptomatic with fatigue, lower back pain, and unintentional weight loss. For this reason, he might prefer agents with a higher chance of a rapid response, like the IO/TKI combination, which might have a slightly higher response rate. If the patient had sarcomatoid features, he would be more tempted to offer an IO-based therapy given the data.

The audience was not inclined to offer a single-agent TKI in this situation. To give that option, Braun said the patient would have to have a strong contraindication to an IO-based therapy. That would include someone with severe and active autoimmune disease, for whom he would not want to give anti-PD-1 therapy. He would also consider it for those with indolent disease biology who could afford to go through active surveillance but might need therapy at some point.

Since quality of life generally improves with greater tumor control, the panel weighed pros and cons of toxicity brought on by using these combinations, especially from TKIs. Ornstein said he generally starts patients on doses from clinical trials, while telling patients that he may need to change the dosing or scheduling. His goal is a deep, durable response, which can lead to some short-term toxicity. He considers the agent's half-life when lowering the dose and potentially giving the patient a break from the regimen. With a drug like cabozantinib, which has a 90-hour or greater half-life, he is more inclined to lower the dose rather than give the patient a break from

it, as resolving toxicity could take more than a week. He may give the patient a break to resolve toxicity from a TKI like axitinib, which has a 4-hour half-life, and then continue the same dose. Ornstein said that for patients on an IO regimen, he usually leaves them on the prescribed dose unless there's an adverse event so severe that the patient needs steroids. He would then reconsider reinitiating that agent.

When managing toxicity, Braun looks for patterns such as whether the patient has a built-up effect from TKIs for which they need a short break from therapy rather than experiencing ongoing and continuous toxicity warranting a dose reduction. Pharmacokinetics and patient-specific adverse effects both play a role. He also emphasizes to patients that decreasing the dose is not a failure and won't necessarily be detrimental to its impact. "It is always good to maximize the amount of medicine that the patient can be on that is tolerable. But the keyword is 'tolerable,' and they should be able to live their lives; it is all about finding that balance for each patient."

### **RCC in the Second-Line Setting**

As for subsequent options, Zhang noted that the METEOR trial (NCT01865747), an early trial in this space comparing cabozantinib and everolimus, hit all its efficacy targets of PFS and OS and resulted in a greater ORR.<sup>10</sup> She said that cabozantinib is a good option in this setting and a viable choice after frontline ipilimumab/nivolumab.

As for therapy choice following frontline IO-based combinations, Ornstein said that current data are sparse for using an IO/TKI combination after progression. If a patient was on an IO/IO combination or IO/TKI combination and had a good response and slow progression, another combination might be considered as it may still be sensitive to the strategy and benefit from the new agents. He would consider changing to a single-agent TKI or to an option like

lenvatinib and everolimus. He would consider moving away from the IO-based regimen in the IO-refractory setting as the immediate next therapy.

Braun was asked to expand upon data from a phase 2 randomized trial of lenvatinib and everolimus as single agents and as a combination in second-line RCC, results of which were published in 2015.<sup>11</sup> Despite the small size of the cohort (n = 153), Braun considers the results to be indicative of a benefit for the combination. "When we look at metrics like response, there seems to be a benefit in favor of lenvatinib plus everolimus." He said the starting dose in the trial of 18 mg lenvatinib and 5 mg everolimus daily can be a lot for patients and most will need reductions.

Braun was asked to discuss the phase 3 TIVO-3 trial (NCT02627963) that led to the approval of tivozanib (Fotivda) for patients with relapsed or refractory RCC after 2 or more prior lines of therapy.<sup>12,13</sup> Patients were to receive the VEGFR TKI tivozanib or sorafenib (Nexavar), which has a broader range of targets beyond VEGFR. The trial was performed in heavily pretreated patients who were potentially beyond the second- or third-line setting. Tivozanib outperformed in terms of both ORR and PFS. "At that point, it is sometimes hard to measure things like overall survival when it is in such late lines of therapy," Braun said.

The ASCO 2021 update revealed that median duration of response to tivozanib was 20.3 months compared with only 9.0 months for sorafenib (HR, 0.55; 95% CI, 0.30-1.00).<sup>14</sup> The hazard ratio for OS also favored tivozanib at 0.91 (95% CI, 0.716-1.165; *P* = .47) but failed to reach statistical significance. Other benefits of tivozanib include its overall tolerability, with similar rates of serious adverse events observed in both tivozanib and sorafenib (11% vs 10%).

### **Case of Second-Line RCC**

Again, the panelists considered this practically with a patient case.

## CASE 2

- A 53-year-old woman with renal cell carcinoma underwent right total nephrectomy in April 2019.
- About 13 months later, she developed metastatic disease to bilateral lung and mediastinum.
- Diagnosis: stage IV RCC, clear-cell histology, no sarcomatoid features
- KPS: 90%
- Laboratory testing is significant for corrected calcium 12 mg/dL and hemoglobin 9.8 g/dL.

In a polling question, 60% of the audience thought this patient had IMDC intermediate-risk disease. Braun agreed, assuming her platelets and absolute neutrophil count were normal, noting that KPS is greater than 80%. It was more than 12 months from disease diagnosis to needing systemic therapy.

## CASE 2 (CONTINUED)

- The patient was treated with a combination of ipilimumab and nivolumab.
- Now, 18 months later, she has disease progression with increasing lung nodules.

As for second-line treatment, Zhang did not see any contraindications for immunotherapies. With intermediate-risk disease in a patient with metastases who is more than a year out from nephrectomy, she would recommend an IO-based combination aiming for a complete response.

After progression, Zhang said multiple options in both the first- and second-line settings make sequencing decisions complex. “We are coming to a point where many of our patients are coming through their first line [of therapy] and we are making this treatment selection. [We

must think about] what mechanisms are we trying to target? What are the patients resistant to from their first line of therapy?”

For her patient, Zhang said she would use cabozantinib based on the METEOR trial based on improved results vs everolimus in terms of OS, PFS, and ORR. Similarly, Ornstein said he would switch to either single-agent TKI or a combination like lenvatinib plus everolimus and get away from IO therapy in a patient who was refractory.

## Closing Remarks

When asked about remaining unmet needs in metastatic RCC, Ornstein said optimizing care using multiple approved agents and combinations will be key. One question in the metastatic setting is regarding the duration of therapy necessary for a patient to have a long-term durable response. With conditional survival data from CheckMate 214 showing nivolumab plus ipilimumab producing progression-free survival times of 3 years and potentially even 5 years,<sup>3</sup> he wonders whether patients can stop 1 or both agents at a certain point.

Although Braun thinks these issues will be helpful for patients, he does not think they will move the needle in terms of higher cure rates for advanced RCC. “Something like that is going to require new targets and new approaches,” he said. “I think those are going to be immunotherapy-based approaches.”

As for advice to share with community practitioners treating advanced RCC, Zhang said she thinks about the entire treatment process including multiple lines of treatment when starting first-line therapy, including what she might use if and when the patient progresses and what they are resistant to. She tries to limit initial use of the most active agent to save broader mechanisms like cabozantinib or lenvatinib for later lines and use an ipilimumab/nivolumab approach or an axitinib/pembrolizumab approach early. In cases where she needs an active agent early for disease control, she’ll go with that approach. It could include a VEGF plus IO

combinations like cabozantinib/nivolumab or lenvatinib/pembrolizumab. ■

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